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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/602,272	02/16/1996	MICHAEL J. ELLIOTT	KIR96-01	4297

7590 09/12/2005

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/602,272	ELLIOTT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 6,8-10,12-32 and 34-50 is/are pending in the application.

4a) Of the above claim(s) 16-28 and 38-50 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 6,8-10,12-15,29-32 and 34-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/29/05+11/9/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 29, 2005 has been entered.

2. Claims 6, 8-10, 12-32 and 34-50 are pending. Claims 16-28 and 38-50 remain withdrawn from consideration. Claims 6, 8-10, 12-15, 29-32 and 34-37 are under consideration.

3.

Sections of Title 35, U.S. Code, not found in this action can be found in a prior action.

4. Claim 15 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim14. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 15 was amended in the filing of Feb 5, 2002 to be dependent on claim 12, thus introducing a duplicate claim.

5. Claims 6, 8-10, 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "preventing thrombosis in a subject diagnosed as suffering from thrombosis". It is unclear how thrombosis can be "prevented" when a subject already suffering from thrombosis. For purpose of examination, claims 6, 8-10, 12-15 will be read as preventing thrombosis or treating a subject diagnosed with thrombosis.

6. Claims 6, 8-10, 12-15, 29-32 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have been amended to incorporate the limitation of "a subject diagnosed as suffering from thrombosis". The specification and claims as filed are drawn to the treatment of thromboembolic disorders, where the thromboembolic disorder includes deep vein thrombosis (original claims 7 and 8). Neither the specification nor the originally filed claims provide support for limiting treatment to subjects "diagnosed" as suffering from thrombosis. Further, neither the specification nor originally filed claims provide support for the broadly claimed treatment of "thrombosis" rather than the treatment of deep-vein thrombosis as recited in the specification and originally filed claims, nor the broadly claimed method of decreasing the level of plasma fibrinogen in a subject as diagnosed with thrombosis. Amendment to broaden the disclosed method of treating "deep venous thrombosis" to a method of treating thrombosis is not supported by the originally filed disclosures in light of the fact that art recognizes numerous molecular defects which cause a subject to be in a prethrombotic state such as inherited as acquired disorders of antithrombin III deficiency, Protein C and S deficiency, Dysplasminogenimia, Dysfibrogenimeia, defective release and diminished venous content of PA, excessive release of PAI, Homocystineurea, chronic congestive heart failure, Metastatic tumors, extensive trauma or major surgery, Myeloproliferative disorders, Behcet's syndrome, Kawasaki's disease, treatment with oral contraceptives and treatment with GM-CSF (Handin, R. 'Disorders of Coagulation and Thrombosis', In: Harrison's Principles of Internal Medicine, 13th Ed., Vol. 1, Isselbacher et al, Ed., pp. 1804-1810, see Table 315-3) and one of skill in the art would not conclude upon reading of the speciation, that the instant method would include the broadly claimed treatment of thrombosis rather than the treatment of deep-venous thrombosis. Further, with respect to claims 29-42 and 34-37, it is noted that the specification contemplates the reduction of fibrinogen levels only in patients with active rheumatoid arthritis (page 2, lines 14-18) and thus fails to support the limitation of reducing the fibrinogen levels in patients with thrombosis or patients diagnosed with thrombosis.

7. Claims 6 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the abstract of Martini et al (Current Therapeutic Research, 1993, Vol. 53, pp. 340-346) or the abstract of Di

Perry et al (Haemostasis, 1986, Vol. 16 Suppl. 1, pp. 42-47), both as evidenced by Bianchi et al (European Journal of Pharmacology, 1993, Vol. 238, pp. 327-334).

Claim 6 is drawn to a method of treating or preventing thrombosis in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. Claim 29 is drawn to a method of decreasing plasma fibrinogen in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. The specification defines TNF antagonists of the instant invention as including compounds which are A2B receptor agonists (page 2, lines 2-8). Bianchi et al indicate that Defibrotide is a competitive inhibitor of NECA (page 329-330, under section 3.1) which is a specific agonist of the A2B receptor. Thus, Defibrotide is a A2B receptor agonist and included with the TNF antagonists of the instant invention.

The abstract of Martini et al discloses a method of treating subjects diagnosed as having retinal vein thrombosis, said method comprising the administration of Defibrotide.

The abstract of Di Perri et al disclose a method of treating thrombosis in patients having acute thrombophlebitis comprising the administration of Defibrotide.

Neither abstract specifically discloses that the administration of Defibrotide decreases the level of plasma fibrinogen, however, Defibrotide is disclosed as having fibrinolytic activity, and therefore the method of treating thrombosis comprising the administration of Defibrotide would inherently result in the decrease in plasma fibrinogen.

8. Claims 6 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by either of the abstracts of Mozzi et al (Haemostasis, 1986, Vol. 16 Suppl. 1, pp. 36-38) or the abstract of Ciavarella et al (Haemostasis, 1986, Vol. 16 Suppl. 1, pp. 39-41), both as evidenced by Bianchi et al (European Journal of Pharmacology, 1993, Vol. 238, pp. 327-334)..

The abstract of Mozzi et al discloses a method of preventing deep venous thrombosis due to general surgery, and the abstract of Ciavarella et al discloses a method of preventing deep venous thrombosis due to gynecological surgery, both methods comprising the administration of Defibrotide. Bianchi et al indicate that Defibrotide is a competitive inhibitor of NECA (page

329-330, under section 3.1) which is a specific agonist of the A2B receptor. Thus, Defibrotide is a A2B receptor agonist and included with the TNF antagonists of the instant invention.

9. Claims 6, 8-10, 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creager et al ('Vascular Diseases of the Extremities', In: Harrison's Principles of Internal Medicine, 13th Ed., Vol. 1, Isselbacher et al, Ed., pp. 1135-1142) in view of Le et al (WO 92/16553, cited in a previous Office action).

The specific embodiments of claims 6 and 29 are recited above. Claim 8 embodies the method of claim 6, wherein the antagonist is an anti-TNF antibody or an antigen-binding fragment thereof. Claim 9 embodies the method of claim 8 wherein the antibody is selected from the group consisting of a humanized antibody, a resurfaced antibody or antigen-binding fragment thereof. Claim 10 embodies the method of claim 8 wherein the antibody bind to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of human TNF alpha. Claim 12 embodies he method of claim 8 wherein the antibody is a chimeric antibody, said chimeric antibody comprising a non-human variable region specific for TNF or an antigen binding portion thereof and a human constant region. Claim 13 embodies the method of claim 12 wherein the chimeric antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of human TNF alpha. Claims 14 and 15 embody the method of claim 12 wherein the antibody competitively inhibits the binding of TNF alpha to monoclonal antibody cA2.

Creager et al teach a method of treating deep-vein thrombosis in a subject diagnosed as having such, the method comprising the administration of anticoagulants (page 1141, second column, lines 13-20) to allow for endogenous fibrinolytic destruction of the thrombus. Creager et al teach disseminated intravascular coagulation as a pre-thrombotic state (page 1140, Table 211-2). Creager et al do not teach the administration of cA2, antibodies which compete with cA2 for binding to TNF alpha or humanized or resurfaced A2 as a anticoagulation agent.

Le et al teach high affinity murine-human chimeric antibodies to TNF which block the procoagulant activity of TNF (page 13, line 37 to page 14, line 4 and page 60, Table 2). Le et al teach that the high affinity antibodies of the invention bind to epitopes of residues 87-107 and 59-80 of human TNF (page 14, lines 13-15). Le et al teach the cA2 antibody as a specific

embodiment of the high affinity chimeric antibodies (page 14, lines 8-12). Le et al teach the treatment of vascular inflammatory pathologies such as disseminated intravascular coagulation by the administration of the anti-TNF antibodies (page 34, lines 17-19).

It would have been prima facie obvious at the time the claimed invention was made to administer cA2 or TNF binding fragments thereof to a patient diagnosed as having thrombosis. One of skill in the art would have been motivated to do so by the teachings of Creager et al on the need to treat individuals with thrombosis with anti-coagulants and the teachings of Le et al on the ability of cA2 to inhibit the procoagulant activity of TNF, as well as the teachings if Creager et al noting the association with disseminated intravascular coagulation and the increased risk of thrombosis and the teachings of Le et al on the treatment of disseminated intravascular coagulation by the administration of the cA2 antibody.

10. Claims 29-32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creager et al ('Vascular Diseases of the Extremities', In: Harrison's Principles of Internal Medicine, 13th Ed., Vol. 1, Isselbacher et al, Ed., pp. 1135-1142) in view of Le et al (WO 92/16553, cited in a previous Office action) as evidenced by Charles et al (Journal of Immunology, 1999, Vol. 163, pp. 1521-1528).

Claim 30 embodies the method of claim 29, wherein the antagonist is an anti-TNF antibody or an antigen-binding fragment thereof. Claim 31 embodies the method of claim 30 wherein the antibody is selected from the group consisting of a humanized antibody, a resurfaced antibody or antigen-binding fragment thereof. Claim 32 embodies the method of claim 30 wherein the antibody bind to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of human TNF alpha. Claim 33 embodies the method of claim 32 wherein the antibody competitively inhibits the binding of human TNF alpha to the monoclonal antibody cA2. Claim 34 embodies he method of claim 30 wherein the antibody is a chimeric antibody, said chimeric antibody comprising a non-human variable region specific for TNF or an antigen binding portion thereof and a human constant region. Claim 35 embodies the method of claim 34 wherein the chimeric antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of human TNF alpha. Claim 36 embodies the method of claim 34 wherein the antibody competitively inhibits the

binding of TNF alpha to monoclonal antibody cA2. Claim 37 embodies the method of claim 34 wherein the chimeric antibody is cA2.

The combination of Creager et al and Le et al render obvious the specific limitation of the claims with respect to the treatment of thrombosis in patients diagnosed as suffering from thrombosis. Neither of Creager et al or Le et al teach the decrease in serum fibrinogen levels, however, it would be inherent in the method of administering the cA2 antibody that serum fibrinogen levels would decrease as evidenced by Charles et al (page 1525, first column, lines 12-17).

11. Claims 6, 8-10, 12-15 are provisonally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of copending Application No. in view of Creager et al ('Vascular Diseases of the Extremities', In: Harrison's Principles of Internal Medicine, 13th Ed., Vol. 1, Isselbacher et al, Ed., pp. 1135-1142) and Le et al (WO 92/16553, cited in a previous Office action)..

Creager et al teach a method of treating deep-vein thrombosis in a subject diagnosed as having such, the method comprising the administration of anticoagulants (page 1141, second column, lines 13-20) to allow for endogenous fibrinolytic destruction of the thrombus. Creager et al teach disseminated intravascular coagulation as a pre-thrombotic state (page 1140, Table 211-2). Creager et al do not teach the administration of cA2, antibodies which compete with cA2 for binding to TNF alpha or humanized or resurfaced A2 as a anticoagulation agent.

Le et al teach high affinity murine-human chimeric antibodies to TNF which block the procoagulant activity of TNF (page 13, line 37 to page 14, line 4 and page 60, Table 2). Le et al teach that the high affinity antibodies of the invention bind to epitopes of residues 87-107 and 59-80 of human TNF (page 14, lines 13-15). Le et al teach the cA2 antibody as a specific embodiment of the high affinity chimeric antibodies (page 14, lines 8-12). Le et al teach the treatment of vascular inflammatory pathologies such as disseminated intravascular coagulation by the administration of the anti-TNF antibodies (page 34, lines 17-19).

This is a provisional obviousness-type double patenting rejection.

12. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
9/6/2005

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